Hereditary angioedema with normal C1 inhibitor function: Consensus of an international expert panel

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ABSTRACT

A new form of hereditary angioedema (HAE) with normal C1 inhibitor (C1INH) was first described in 2000. The lack of clear diagnostic criteria, the heterogeneity among affected patients, and the varying names given to this disease have led to substantial confusion among both physicians and patients. This study was designed to bring more clarity to the diagnosis and potential treatment of HAE with normal C1INH. An international symposium of experts was convened to review the field and develop consensus opinions that could help clinicians who evaluate and manage these patients. Criteria were developed for the diagnosis of HAE with normal C1INH in patients with recurrent angioedema in the absence of concurrent urticaria. In addition, potential therapeutic strategies are discussed. The consensus criteria developed during this symposium will allow physicians to better diagnose and treat patients with HAE with normal C1INH.

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Hereditary angioedema (HAE) was first described by William Osler in 1888 as recurrent angioedema that affected multiple generations within families. Donaldson identified the pathological basis of HAE as a deficiency of C1 inhibitor (C1INH) in 1963.[1] Two years later, Rosen described a second form of HAE in which C1INH protein levels were normal but the function was deficient.[2] Our understanding of HAE as a disease caused by C1INH deficiency remained intact until 2000 when two separate groups described families showing a dominant inheritance of recurrent angioedema with normal or near normal C1INH.[3,4] This disorder has variously been called "new HAE," "estrogen-dependent HAE," "type III HAE," "HAE with normal C1INH," and "familial angioedema with normal C1INH." Mutations in the coagulation factor XII (fXII) gene (*F12*) have been identified in a minority of affected families; however, the cause of the disease has remained elusive in the majority of families.

In the 12 years since the original description of this disease, there has been relatively little progress made in developing diagnostic criteria or therapeutic guidelines. Indeed, confusion regarding how to differentiate acquired angioedema of unknown cause from HAE with normal C1INH function has become a significant clinical issue leading to both failures to make the proper diagnosis and misdiagnosis of many patients. This confusion has frustrated both patients and physicians. Furthermore, lack of clear diagnostic criteria and controlled studies in HAE with normal C1INH have limited the number of investigational studies on this form of HAE and prevented development of therapeutic guidelines for this disease.

In response to this situation, the U.S. HAE Association sponsored a 1-day symposium devoted to HAE with normal C1INH function. A group of clinical and scientific investigators in HAE from North America and Europe were invited by the Co-Chairs (K.B. and B.Z.) to participate in this symposium based on their expertise in various areas of relevance to the discussion. The attendees undertook a systematic review of HAE with normal C1INH: reviewing what is known

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Table 1 **Classification of recurrent angioedema without urticaria or other associated disorder**

Pattern	Name	Subtype	Comment
Familial			
	HAE due to C1INH deficiency	Type I	Caused by mutation of *SERPING1* leading to functional C1INH deficiency; bradykinin mediated
		Type II	Caused by mutation of *SERPING1* leading to functional C1INH deficiency; bradykinin mediated
	HAE with normal C1INH	fXII Mutation	Associated with mutations in fXII; likely bradykinin mediated
		Unknown cause	Genetic mutation is unknown; likely bradykinin mediated
Sporadic			
	Acquired C1INH deficiency	—	Associated with underlying malignancy or disease or anti-C1INH autoantibody that results in increased catabolism of C1INH; bradykinin mediated
	ACE-I related	—	Decreased catabolism of bradykinin; likely bradykinin mediated
	Allergic	—	Mast cell degranulation involving specific IgE
	Unknown etiology	Histaminergic	Mast cell degranulation
		Nonhistaminergic	Possibly bradykinin-mediated

ACE-I = angiotensin-converting enzyme inhibitor; C1INH = C1 inhibitor.

about the disease; identifying gaps in our understanding; developing concrete criteria for the diagnosis of the disease; and, finally, proposing an agenda to close these gaps. This article represents the discussion and consensus of this group and is divided into the following eight sections: (1) nomenclature of HAE, (2) clinical features of HAE with normal C1INH function patients, (3) clinical impact of estrogens on HAE with normal C1INH, (4) *F12* mutations and HAE with normal C1INH, (5) pathophysiology of HAE with normal C1INH, (6) diagnosis of HAE with normal C1INH, (7) therapeutic experience in patients with HAE with normal C1INH, and (8) conclusions and future directions.

NOMENCLATURE OF HAE

Key Points

The name of this disease should be standardized as HAE with normal C1INH.

The name type III HAE should not be used because it does not convey either the fundamental difference from HAE due to C1INH deficiency or the fact that there are subtypes within the group of patients with HAE with normal C1INH.

The name estrogen-dependent HAE should not be used because it does not convey the fact that most of the affected patients are not strictly estrogen dependent.

The nomenclature of HAE due to C1INH deficiency is both clear and well established. In contrast, HAE with normal C1INH has been referred to by multiple names, including new HAE, estrogen-dependent HAE, and type III HAE. Consensus was reached regarding a suggested nomenclature of recurrent angioedema without urticaria or other associated disorder (Table 1). There was unanimous agreement that HAE should be divided into two categories: HAE due to C1INH deficiency and HAE with normal C1INH. Within the HAE due to C1INH deficiency category, two subtypes are defined: type I HAE (with low C1INH antigen and function) and type II HAE (with normal C1INH antigen but low C1INH function). Within the HAE with normal C1INH category, two subtypes are also defined: HAE with normal C1INH and *F12* mutation and HAE with normal C1INH of unknown cause. It was strongly recommended that the name type III HAE not be used because it is suspected that this group of patients may have a variety of pathological mechanisms resulting in a common phenotype.

CLINICAL FEATURES OF HAE WITH NORMAL C1INH

Key Point

Although the clinical features of HAE with normal C1INH are similar to those of HAE due to C1INH

Table 2 **Phenotypes of HAE due to C1INH deficiency and HAE with normal C1INH**

Finding	HAE Due to C1INH Deficiency	HAE with Normal C1INH
Average age of symptom onset	11.7 ± 7.7 yr	26.8 ± 14.9 yr
Gender	Female = Male	Female > Male
Attack location		
Abdominal	Almost all patients experience	50% of Patients experience
Facial	Occasional	Common
Tongue	Not common	Common
Erythema marginatum	Common	Not seen
Multiorgan attacks	Common	Uncommon
Disease-free intervals	Generally short	May be considerable
Penetrance	Generally high; rare asymptomatic carrier	Generally low; may see obligate asymptomatic carrier

C1INH = C1 inhibitor; HAE = hereditary angioedema.

deficiency, a number of small but significant differences distinguish these forms of HAE.

HAE with normal C1INH is characterized by recurrent angioedema that is transmitted through multiple generations in affected families.[3–5] Attacks are prolonged and can cause asphyxiation.[6] Attack frequency varies considerably between affected individuals, from asymptomatic carriers to patients with multiple attacks per year. States of increased estrogen exposure due to either pregnancy or exogenous estrogen administration frequently exacerbate the disease (see the following section). The earliest reports of HAE with normal C1INH identified only women; however, it has subsequently become clear that men may also be affected.[7,8] Despite the finding of some symptomatic men, the female preponderance of patients remains striking, and affected women tend to have more severe symptoms than affected men. Examination of large pedigrees suggested an autosomal dominant inheritance. Unlike HAE due to C1INH deficiency, the inheritance pattern of HAE with normal C1INH shows a variable but sometimes low penetrance with evidence of obligate asymptomatic carriers, particularly men.

The largest cohort of HAE patients with normal C1INH has been reported by Bork, who has described the clinical features of the disease in 138 patients from 43 families.[6] Almost all of his patients experienced skin swellings, with facial swelling being quite common. In contrast, only 50% of the subjects had ever experienced an abdominal attack. Over 50% of the subjects had experienced tongue swelling with laryngeal angioedema reported in ~25% of subjects. Of note, four affected relatives of the subjects had suffocated because of an upper airway obstruction. Many of the attacks involved only one location, and erythema marginatum was not observed. The mean age of onset was 26.8 ± 14.9 years with the only 8% of subjects experiencing their first attack during the first decade of life. Angiotensin-converting enzyme inhibitors (ACE-I) worsen disease in both HAE due to C1INH deficiency as well as HAE with normal C1INH.[7,9] In addition, angiotensin receptor blockers have been reported to worsen disease in HAE with normal C1INH patients who received an angiotensin receptor blocker.[10] The clinical features that distinguish HAE with normal C1INH from HAE due to C1INH deficiency are summarized in Table 2.

CLINICAL IMPACT OF ESTROGENS IN HAE WITH NORMAL C1INH

Key Points

Estrogens exacerbate disease severity in most but not all patients with HAE with normal C1INH.
A subset of these patients show swelling that is strictly estrogen dependent.
Pregnancy has a variable impact on disease severity.

As the clinical experience with HAE with normal C1INH has increased, it has become clear that there is significant variability in the impact of estrogens on disease activity. In the original reports of HAE with normal C1INH,[3–5] all of the patients were women. The family reported by Binkley and Davis[4] showed a strict estrogen dependence of swelling episodes, in that the affected women reproducibly swelled at times of increased exposure to estrogen and never swelled when they were not pregnant or taking an estrogen-containing medicine. In contrast, estrogens worsened the angioedema in the patients described by Bork, but most of the women had episodes of swelling even when not pregnant or not taking an estrogen-containing medicine.[3] Subsequently, many women have been reported with HAE with normal C1INH in whom estrogens appear to have no impact on their disease.[7,11–13] Table 3

Table 3 **Estrogen impact on disease severity in HAE with normal C1INH**

First Author	No. Patients	No. Families	Required for Sx	Worsens Sx	No Impact on Sx	Unknown	Reference
Binkley	7	1	7	0	0	0	4
Martin	4	1	3	1	0	0	5
Bork	35	13	20	10	5	0	74
Vitrat-Hincky	22	15	5	12	4	1	12
Bouillet	2	1	0	2	0	0	24
Picone	6	2	6	0	0	0	20
Martin	2	1	0	2	0	0	8
Serrano	10	5	10	0	0	0	53
Prieto	4	1	4	0	0	0	54
Baeza	3	1	3	0	0	0	55
Total	95	41	58	27	9	1	

C1INH = C1 inhibitor; HAE = hereditary angioedema; Sx = symptoms.

summarizes the clinical impact of exogenous estrogens and pregnancy on disease activity in women with HAE with normal C1INH. Although estrogens may also worsen other types of swelling, including HAE due to C1INH deficiency, only HAE with normal C1INH has shown evidence of strict estrogen dependence or evidence of obligate male carriers.

Pregnancy has a variable impact on disease severity, both in HAE due to C1INH deficiency and in HAE with normal C1INH.[14–19] In fact, the effect of pregnancy on angioedema symptoms in HAE patients can vary considerably from one pregnancy to the next, even in the same patient. Picone *et al.* reported two distinct families with HAE with normal C1INH associated with an *F12* mutation (Thr309Lys) in which the affected women experienced severe complications of their disease during pregnancy, including fetal and neonatal death.[20] In both of these families, angioedema attacks occurred only during pregnancy or use of estrogen-containing medications.

The mechanism by which pregnancy leads to increased disease activity in HAE is complex. Levels of sexual hormones that may impact disease severity (such as estrogens, progestins, and androgens) vary during pregnancy. Pregnancy is associated with a significant decrease in steady-state levels of C1INH even in normal women.[21–23] Development of transient C1INH deficiency during pregnancy has been documented in some women with HAE with normal C1INH who experience increased episodes of angioedema.[20,24] In one case, the decrease in functional C1INH was correlated with cleavage of C1INH into its inactive fragment.[24] C1INH function returned to normal after delivery in all of these cases. Considering that activation of the plasma contact system has been shown to cause cleavage of C1INH,[25] it is not clear whether the fall in functional C1INH level is a cause or consequence of the increased angioedema attacks in these cases.

F12 MUTATIONS AND HAE WITH NORMAL C1INH

Key Points

_F12_ mutations are found in a minority of patients with HAE with normal C1INH, but when present cosegregate with disease.

Evidence of asymptomatic _F12_ mutation carriers suggest an autosomal dominant inheritance with incomplete penetrance.

Haplotype analysis points to a distant European founder effect for the most common 1032C → A (Thr309Lys) _F12_ mutation.

The codon 309 _F12_ mutations appear to be relatively rare in HAE with normal C1INH patients in the United States.

In 2000, Binkley and Davis sequenced the *SERPING1* gene that encodes C1INH and found no mutations in their subjects with HAE with normal C1INH. They also sequenced the 5′ promoter region of *F12* but failed to identify any mutations. Bork and colleagues used a candidate gene approach, beginning with fXII. They identified mutations in the proline-rich region of *F12* in 6 of 20 kindreds with HAE with normal C1INH.[26] Two separate nonconservative mutations were identified, 1032C → A (Thr309Lys) in 5 unrelated patients and 1032C → G (Thr309Arg) in 1 patient but not in 145 unrelated normal controls. Family members in 5 of the kindreds were tested for the mutation, and the mutation was found to cosegregate with the disease. All 20 individuals with HAE with normal C1INH were found to be heterozygous for the *F12* mutation. In addition, two asymptomatic women and eight asymptomatic men were also found to be heterozygous for the mutation. The inheritance strongly suggested an autosomal dominant pattern with incomplete penetrance. The 1032C → A (Thr309Lys) mutation was also re-

Table 4 **Factor XII mutations in HAE with normal C1INH**

First Author	No. Families	No Mutation Found	Thr309Lys	Thr309Arg	Other Mutation	Reference
Dewald	20	14	5	1	0	26
Duan	1	0	1	0	0	72
Bouillet	1	0	1	0	0	24
Baeza	1	0	0	0	1	55
Nagy	1	0	1	0	0	46
Prieto	1	0	1	0	0	54
Cichon	1	0	1	0	0	27
Vitrat-Hincky	15	12	3*	0	0	12
Picone	2	0	2	0	0	20
Martin	1	0	1	0	0	8
Bork	53	40	11	2	0	74
Bork	1	0	0	0	1	28

**fXII Thr309Lys vs Thr309Arg mutation not specified.*
C1INH = C1 inhibitor; HAE = hereditary angioedema.

ported by Cichon *et al*.[27] Haplotype analysis in four affected kindreds suggested a distant common founder, suggesting that this mutation may be relatively specific to patients who descended from a distant European mutation.[27] Subsequently, a number of additional patients have been found with these same *F12* mutations, which is reported to occur in up to 25% of Europeans with HAE with normal C1INH.[26] These *F12* mutations appear to be rare within the U.S. patient population. Recently, a unique *F12* mutation was found in a Turkish family diagnosed with HAE with normal C1INH.[28] This was a 72-bp deletion (c.971_1018 + 24del72*) that also involves the proline-rich region of *F12*. Table 4 reviews the reported *F12* mutations in patients with HAE with normal C1INH.

Taken together, there is abundant evidence that several *F12* mutations are causally linked to a subset HAE with normal C1INH patients because of a functional effect on fXII. The exact nature of the functional alteration remains unclear at the current time. Importantly, no clinical features have emerged that distinguish HAE with normal C1INH patients who do not have an *F12* mutation from those who do have an *F12* mutation. Similarly, no differences have been noted between patients with the Thr309Lys and Thr309Arg mutations, although the latter mutation is only known to involve a small number of patients.

PATHOPHYSIOLOGY OF HAE WITH NORMAL C1INH

Key Points

The lack of efficacy of antihistamines and corticosteroids as well as the anecdotal efficacy of drugs used to treat HAE due to C1INH deficiency suggest that the mediator of swelling is bradykinin.

Factor XII is a key protease in contact system activation and the production of bradykinin.

Mutations in *F12* associated with the disease have been suggested to increase *ex vivo* contact system activation.

Estrogens have a variety of effects on the contact system that may enhance the generation of bradykinin as well as its bioactivity.

Little is currently known about the pathophysiology of HAE with normal C1INH. Three aspects of the disease that may point to important pathophysiological processes are the response to therapeutic drugs, the role of *F12* mutations, and the impact of estrogens on disease severity. Taken together, these factors strongly implicate bradykinin as the mediator of swelling in HAE with normal C1INH. The details regarding the fundamental pathophysiology of bradykinin-mediated angioedema, including the relative contributions of increased generation of bradykinin, decreased catabolism of bradykinin, or altered bradykinin signaling still need to be elucidated.

The failure of antihistamines and corticosteroids to alter the swelling in HAE with normal C1INH has been consistently observed and has become part of the diagnostic criteria for this disease. These observations suggest that the pathophysiology of HAE with normal C1INH does not involve histamine or mast cell degranulation. In addition, drugs that have proven to be efficacious in HAE due to C1INH deficiency (17α-alkylated androgens, tranexamic acid, C1INH concentrates, icatibant, and ecallantide) appear in uncontrolled observational reports to be helpful in a large

majority of HAE with normal C1INH patients. Activation of the plasma contact system with generation of bradykinin has been shown to be the major cause of swelling in HAE due to C1INH deficiency,[25,29–36] and these drugs are thought to interfere with the generation, catabolism, or signaling of bradykinin.[37–39]

The discovery of *F12* mutations linked to the inheritance of HAE with normal C1INH represented a key advance in our understanding of this disease with important pathophysiological implications. Coagulation fXII is a zymogen serine protease that is part of the intrinsic coagulation system and initiates plasma contact system activation when plasma is exposed to a negatively charged surface or a variety of other activating signals.[40,41] A conformational change in zymogen fXII renders it a substrate for minute amounts of active fXII (fXIIa), which cleaves the zymogen serine protease plasma prekallikrein to generate active plasma kallikrein. Active plasma kallikrein reciprocally activates additionally both fXII to fXIIa and fXIIa to fXIIf. Active plasma kallikrein also cleaves its binding partner high molecular weight kininogen, releasing bradykinin. C1INH regulates fXIIa, fXIIf, and plasma kallikrein activity. Thus, deficiency of C1INH results in excessive activation of the plasma contact system with generation of bradykinin, the major mediator of swelling in HAE due to C1INH deficiency. Factor XII is also activated by misfolded proteins and appears to be part of the resulting inflammatory response.[42]

Any abnormalities that lead to enhanced activation of fXII would be expected to result in increased bradykinin generation. The mechanisms by which the *F12* mutations linked to HAE with normal C1INH might result in fXII activation remain unclear. Factor XII has a complex organization.[43] The *F12* mutations described, to date, all involve the proline-rich region of fXII rather than the C-terminal catalytic serine protease domain. This proline-rich region could play a role in the binding of fXII to negatively charged surfaces; however, it remains poorly characterized.[44,45]

The functional consequences of the *F12* 1032C → A (Thr309Lys) mutation was assessed by measuring plasma amidolytic activity against the chromogenic substrate DPro-Phe-Arg-*p*-nitroanilide (S2302) in four subjects carrying the mutation compared with controls without the mutation.[27] S2302 is cleaved by several plasma serine proteases, including fXIIa, fXIa, and plasma kallikrein. Median plasma amidolytic activity was found to be increased more than fourfold in the samples with the 1032C → A (Thr309Lys) mutation relative to the controls. Furthermore, the increased amidolytic activity was abrogated by H-D-Pro-Phe-Arg-chloromethylketone, a fXII and plasma kallikrein inhibitor. These results suggested that the *F12* Thr309Lys mutation conferred increased fXII activity, either through enhanced activation or decreased susceptibility to inhibition. In either case, the presumption is that the mutation leads to increased contact system activation and increased bradykinin generation.[46] A subsequent study, however, failed to find evidence for a gain of function in plasma from subjects with the Thr309Lys mutation,[47] and also failed to replicate the increased amidolytic activity. Although not documented in the publication, the Cichon study used Thr309Lys plasma obtained during a period when the patients were highly symptomatic whereas the Bork study used Thr309Lys plasma obtained at time when the patients were free of symptoms. Unpublished data suggest that patients carrying the 1032C → A (Thr309Lys) mutation show enhanced fXII activity in the 24 hours leading up to an angioedema attack, which then returns to normal after the attack (Drouet C, Université Joseph Fourier, Grenoble, France personal communication). This suggests the possibility that the mutation may be associated with a dysregulation of fXII activation rather than a true gain of function, consistent with the fact that the mutation does not involve the catalytic domain of fXII. It is clear that more comprehensive studies are needed to resolve this issue.

The impact of elevated estrogen levels on increasing disease activity in patients with HAE with normal C1INH is abundantly documented but poorly understood. Sex hormones are well known to have a significant impact on other forms of angioedema, most notably HAE due to decreased C1INH where 17α-alkylated androgens generally ameliorate angioedema symptoms and estrogens frequently (but not always) exacerbate symptoms.[48–51] Small anecdotal studies have reported improvement in HAE with normal C1INH patients placed on 17α-alkylated androgens.[3,5,52] The impact of elevated estrogen levels on increasing disease activity has been suggested by a several observations. First, many women with HAE with normal C1INH experience increased swelling during times when they either receive exogenous estrogens (estrogen-containing oral contraceptive pills or hormone replacement therapy) or during periods of endogenously increased estrogen levels, particularly pregnancy.[3–5,12,24,53–55] In addition, the increased frequency and severity of swelling in women with HAE with normal C1INH compared with men suggests a hormonal influence on disease activity. The tendency for HAE with normal C1INH to manifest at an older age than HAE due to C1INH deficiency may be caused by in part the increase in hormones after puberty; however, some children with HAE with normal C1INH have been reported who began to swell before puberty.

A number of mechanisms have been described that may account for the impact of estrogens or pregnancy to increase swelling. Estrogens have a variety of effects on the kallikrein–kinin system. The best-described ef-

Table 5 **Complement values in angioedema**

Type	Subtype	C4	C1INH Antigen	C1INH Function	C1q
HAE due to C1INH deficiency	Type I	Low	Low	Low	Normal
	Type II	Low	Normal	Low	Normal
HAE with normal C1INH	fXII Mutation	Normal	Normal	Normal	Normal
	Unknown cause	Normal	Normal	Normal	Normal
Acquired C1INH deficiency	—	Low	Low	Low	Low
ACE-I related	—	Normal	Normal	Normal	Normal
Allergic	—	Normal	Normal	Normal	Normal
Unknown etiology	Histaminergic	Normal	Normal	Normal	Normal
	Nonhistaminergic	Normal	Normal	Normal	Normal

ACE-I = angiotensin-converting enzyme inhibitor; C1INH = C1 inhibitor; HAE = hereditary angioedema.

fect of estrogen on the kallikrein–kinin system is to significantly increase fXII levels and activity. Gordon *et al.* and Ratnoff indicated increased levels of fXII in the liver of estrogen-treated rats.[56,57] Campbell *et al.* and Fossum *et al.* then showed increased plasma fXII levels in women treated with estrogens.[58–60] The promoter region of the fXII gene has been shown to contain an estrogen-response element, and estrogens have been shown to increase transcription of fXII.[61,62] The clinical relevance of the estrogen-mediated increase in fXII is further suggested by the association between *F12* mutations and HAE with normal C1INH (reviewed previously). Moreover, estrogen has been shown to decrease the expression of C1INH[63] and increase the expression of the kininogenase tissue kallikrein.[64]

In addition to their effects that may lead to increased generation of bradykinin, estrogens have also been shown to enhance bradykinin signaling.[65,66] The mechanism underlying the increased signaling appears to be caused by a combination of estrogen-mediated increased bradykinin B2-receptor expression[67] as well as decreased kininase activity.[68–70] In contrast, 17α-alkylated androgens have been shown to increase the expression of the kininase aminopeptidase P.[71] Interestingly, the family reported by Binkley and Davis[4] experienced angioedema only in a reproducible and strictly estrogen-dependent fashion. The affected members of this family not only had the 1032C $\rightarrow$ A (Thr309Lys) *F12* mutation but also were found to have both an ACE insertion polymorphism and an aminopeptidase P-regulatory polymorphism,[72] both of which result in decreased kininase activity. Thus, it is not unexpected that estrogens may increase angioedema because they have a number of different actions on the kinin system that can increase bradykinin generation, slow the catabolism of bradykinin, and enhance bradykinin receptor signaling.

DIAGNOSIS OF HAE WITH NORMAL C1INH

Key Points

The diagnosis of HAE with normal C1INH should only be made when patients meet the following specific defined criteria:

1. **A history of recurrent angioedema in the absence of concomitant hives or concomitant use of a medication known to cause angioedema.**
2. **Documented normal or near normal C4, C1INH antigen, and C1INH function.**
3. **One of the following:**

Demonstration of a *F12* mutation that is associated with the disease.

A positive family history of angioedema and documented evidence of lack of efficacy of chronic high-dose antihistamine therapy (cetirizine at 40 mg/day or the equivalent, for at least 1 month and an interval expected to be associated with three or more attacks of angioedema).

The diagnosis of HAE with normal C1INH remains challenging. This has resulted both in patients with the disease remaining undiagnosed (with the attendant risks of mistreated angioedema attacks) and in patients who probably do not have the disease being inappropriately diagnosed (with the attendant problems of undo fear and misuse of medications). To partially overcome these problems, the diagnosis of HAE with normal C1INH should be limited to patients who meet a specific and clearly defined set of criteria.

The possibility of HAE with normal C1INH must be considered in the differential diagnosis of recurrent angioedema without concomitant urticaria. The diagnosis of HAE due to C1INH deficiency requires relatively straightforward complement testing. Unfortunately, there are no routinely available laboratory tests that can be relied on to make an unequivocal diagnosis of HAE

with normal C1INH at the current time. Table 5 summarizes the complement profiles of the major forms of recurrent angioedema. As can be appreciated from this table, it is relatively easy to distinguish HAE with normal C1INH from HAE due to C1INH deficiency. The major challenge is distinguishing HAE with normal C1INH from unknown or sporadic angioedema.

Idiopathic angioedema without accompanying urticaria itself is a poorly defined diagnosis and is typically made based on diagnosis by exclusion. Zingale *et al.* reviewed the differential diagnosis of 776 subjects referred for symptoms of recurrent angioedema without concomitant urticaria.[73] Patients underwent a comprehensive battery of tests to identify causative abnormalities, including complement, allergic, autoimmune, and infectious evaluations. C1INH deficiency was identified in 197 of the subjects (25%), including 183 HAE due to C1INH deficiency and 14 due to acquired C1INH deficiency. It is noteworthy that this study did not identify a single HAE with normal C1INH in 776 consecutive patients, reflecting how rare this disease is. Angioedema due to ACE inhibitors was diagnosed in another 85 patients (11%). An additional 179 subjects (23%) were diagnosed with angioedema due to either autoimmune disease or infection (55 subjects) or related to a specific factor such as medications or food (124 subjects). Peripheral edema rather than angioedema was diagnosed in 21 subjects (3%). That remaining 294 subjects (38%) were considered idiopathic or unknown cause. Among the idiopathic angioedema population, 254 responded to high-dose antihistamines. The remaining 40 subjects were unresponsive to high-dose antihistamines and would be considered to fall within the nonhistaminergic angioedema of unknown cause category discussed later. Idiopathic angioedema may also be less likely than HAE with normal C1INH to manifest with tongue or abdominal angioedema.

Fundamentally, the most important diagnostic issue may be to separate nonhistaminergic or bradykinin-mediated angioedema from histamine/mast cell–mediated angioedema. Bradykinin-mediated angioedema tends to be of longer duration, greater severity, more likely to involve the gastrointestinal tract, and much more likely to result in asphyxiation than histamine/mast cell–mediated angioedema. Critically, bradykinin-mediated angioedema does not respond to treatment with antihistamines or corticosteroids. In the absence of sensitive and specific tests to separate these cases, response to treatment may be informative. Thus, clinical improvement with an adequate course of high-dose antihistamines may suggest a histamine/mast cell–mediated basis for the angioedema and lead to a diagnosis of idiopathic histaminergic angioedema. Assessing the response to drugs that act on the contact system (such as C1INH, ecallantide, or icatibant) may be equally valid; however, cost and reimbursement issues have limited our ability to do this.

Based on these considerations, there was unanimous agreement that the diagnosis of HAE with normal C1INH should only be made when patients meet the following specific defined criteria:

1. A history of recurrent angioedema in the absence of concomitant hives or concomitant use of a medication known to cause angioedema.
2. Documented normal or near normal C4, C1INH antigen, and C1INH function.
3. One of the following:

Demonstration of a *F12* mutation that is associated with the disease.

A positive family history of angioedema and documented evidence of lack of efficacy of chronic high-dose antihistamine therapy (cetirizine at 40 mg/day or the equivalent, for at least 1 month and an interval expected to be associated with three or more attacks of angioedema).

Additional weight should be given to some of the clinical features of HAE with normal C1INH such as the predilection to be exacerbated by estrogens and the tendency to involve the face, tongue, and upper airway.

An adequate workup of a patient with suspected HAE with normal C1INH should include a complete history and physical, accurate complement testing, tests to rule out other underlying autoimmune or infectious causes if suggested by the history or physical, a trial of antihistamines including high-dose antihistamines, and an evaluation for *F12* mutations.

The authors recognize that this definition is not perfect, and the limitations of this definition of HAE with normal C1INH need to be recognized. Most importantly, nonhistaminergic idiopathic angioedema may not be able to be absolutely distinguished from HAE with normal C1INH unknown type at the present time. It is clearly possible that some patients may be the first in their family with a disease-causing *de novo* mutation or that other affected family members are asymptomatic because of the low penetrance of the disease. Hopefully, additional laboratory or genetic markers will be found that will improve the ability to make the diagnosis. Nevertheless, this definition represents the best available strategy for identifying HAE with normal C1INH at the current time. This definition should be considered a work-in-progress and updated as additional information becomes available.

THERAPEUTIC EXPERIENCE IN PATIENTS WITH HAE WITH NORMAL C1INH

Key Points

There have been no randomized or controlled clinical trials of therapy for HAE with normal C1INH.

Angioedema attacks in patients with HAE with normal C1INH do not respond to either corticosteroids or antihistamines, even at high doses.

Prophylactic use of 17α-alkylated androgens, the antifibrinolytic drug tranexamic acid, or progestins have shown promising results in some but not all patients.

There is relatively little experience regarding the efficacy of on-demand C1INH, icatibant, or ecallantide in HAE with normal C1INH; however, anecdotal reports suggest that each of these agents may be beneficial.

Until data from randomized controlled studies become available, no firm recommendations regarding the treatment of HAE with normal C1INH can be made.

Although there have not been any prospective studies published, a number of observational open-label reports have assessed the efficacy of various medications for the treatment of HAE with normal C1INH. There is unanimity that angioedema attacks in patients with HAE with normal C1INH do not respond to either corticosteroids or antihistamines, even at high doses.

Because of their established benefit in HAE due to C1INH deficiency, many investigators have treated patients with HAE with normal C1INH with medicines that have been successfully used for the treatment of HAE due to C1INH deficiency. Prophylactic use of 17α-alkylated androgens and the antifibrinolytic drug tranexamic acid have each shown promising results in some but not all patients. Danazol appeared to decrease or prevent attacks in many HAE with normal C1INH patients[3,5,6,52,74]; however, patients were also reported who failed to improve with danazol.[3] Similarly, tranexamic acid has been reported to be helpful in many patients,[6,12,24,53,74] while other patients fail to benefit.[3,8] The known ability of plasmin to activate fXII[75] provides a potential mechanism to account for the efficacy of the plasminogen activation inhibitors tranexamic acid or ε-aminocaproic acid. Interestingly, progesterones have been reported to be both well tolerated[53] and effective in long-term prophylaxis.[7,74]

The effectiveness of on-demand C1INH to treat attacks of angioedema in patients with HAE with normal C1INH is mixed. Some patients appear to do well,[12,74] and others fail to benefit.[3,74] Relatively fewer patients with HAE with normal C1INH have been treated with icatibant or ecallantide; however, those who have are reported to have benefited.[76–78] Interestingly, the response to self-administered icatibant was shown to be slower in HAE with normal C1INH (median time to first improvement, 40 minutes, and complete resolution, 24 hours) compared with HAE due to C1INH deficiency (median time to first improvement, 15 minutes, and complete resolution, 5 hours).[77] Two of the 19 attacks treated in patients with HAE with normal C1INH could be classified as not responding to icatibant based on a time of initial improvement of $\geq$4 hours. Finally, 22% of attacks in patients with HAE due to C1INH deficiency required a second administration of icatibant compared with 37.5% of attacks in patients with HAE with normal C1INH.

The fact that there have been no randomized studies and only a single prospective study of treatment of patients with HAE with normal C1INH means that the available data must be interpreted with caution. In addition, variability in case definition as well as differing parameters of response further complicates the data. It is important that future studies carefully define how subjects are diagnosed, use clear accepted measures of response, and use prospective (ideally randomized) designs. Time to complete resolution as well as angioedema scores at baseline, 1, 2, 4, and 24 hours ought to be routinely reported. Similarly, reduction in attack frequency and severity should be measured in randomized prophylactic trials. Response to treatment may itself be useful for classifying patients, especially the patients with nonhistaminergic angioedema of unknown cause. Until data from such studies become available, no firm recommendations regarding the treatment of HAE with normal C1INH can be made.

CONCLUSIONS AND FUTURE DIRECTIONS

The expert panel meeting reviewed much of the information that has been learned in the 12 years since the original reports of HAE with normal C1INH. Unfortunately, many of the critically important questions about this disease remain unknown, including how to make an accurate diagnosis, what the underlying pathophysiology that results in angioedema is, and how to treat the disease.

The lack of unequivocal diagnostic parameters for making a diagnosis of HAE with normal C1INH presents difficulties for physicians and is extremely frustrating for patients. As shown in Table 2, the phenotype of patients with HAE with normal C1INH reveals subtle differences from that seen in patients with HAE due to C1INH deficiency. Complement and C1INH levels are useful to exclude C1INH deficiency but can not be used to confirm the diagnosis of HAE with normal C1INH. *F12* mutations have been found in a minority of patients, but the vast majority of patients have no genetic marker at this time. Consensus diagnostic criteria for making the diagnosis of HAE with normal C1INH have been developed in this document and provide a useful tool for the practicing physician. The lack of a positive test to confirm the diagnosis in most patients is a significant limitation of these criteria. It is essential that more definitive genetic, molecular, or biochemical markers for this disease be identified and validated.

The true prevalence of this disease is unknown. Large surveys of patients with a history of recurrent angioedema suggest that the disease is extremely rare, no more than 10–20% the prevalence of HAE due to C1INH deficiency.[3,73] Despite its rarity, many allergists report seeing large numbers of patients who believe that they have HAE with normal C1INH. We propose that the diagnostic criteria in this article be used to identify cases that are likely HAE with normal C1INH. Patients who do not meet the current criteria for a diagnosis of HAE with normal C1INH should be further characterized to exclude other causes for the angioedema and to identify the likely mediator of swelling. Distinguishing histamine-mediated angioedema from nonhistaminergic or bradykinin-mediated angioedema is vitally important because of the vastly different prognostic and therapeutic implications of these two pathophysiological processes. Although it is not possible to definitively identify a bradykinin-mediated process at this time, excluding a histamine-mediated process is feasible and extremely important.

Studies are needed to evaluate contact system activation and bradykinin generation under a range of activating conditions as well as the rate of bradykinin degradation in carefully selected populations of HAE with normal C1INH with *F12* mutations and HAE with normal C1INH unknown type. In patients with *F12* mutations, the activity of the fXII proteases needs to be assessed as well as the Ki of their inhibition by C1INH. It would not be surprising if the mechanisms underlying bradykinin-mediated angioedema are heterogeneous among patients with HAE with normal C1INH. Improved assays to measure activation of the contact system, generation of bradykinin, and degradation rates of bradykinin will provide key confirmatory tools for the diagnoses of both HAE with normal C1INH and sporadic bradykinin-mediated angioedema.

A number of medicines have been reported to be helpful in treating attacks of angioedema in patients with HAE with normal C1INH. Unfortunately, most of these reports are anecdotal and all are open label. Randomized clinical studies need to be performed to learn which drugs are truly effective for the treatment of HAE with normal C1INH. We propose that these studies should best be performed using subjects with an unequivocal diagnosis of HAE with normal C1INH.

Progress in each of these areas will require that investigators have access to a large group of patients with HAE with normal C1INH. Considering the rarity of this disease, logistical barriers to access is likely to severely restrict progress. One solution to this conundrum is to create national or international registries that encompass patients recruited from a broad population base and use pooled clinical data and samples. To this end, the U.S. HAE Association and its Medical Advisory Board have developed a patient-centric Angioedema Registry and Bio-Repository specifically to enhance research and investigation on the various forms of recurrent angioedema. The registry contains extensive clinical data that are linked to DNA and plasma samples from the patients. Clinical data in the registry consists of historical data, periodic assessments of status, and per attack data that include information about attack severity and response to treatment consistent with the recently published guidelines.[39] The data and banked samples will be made available to qualified investigators in a coded deidentified fashion to allow studies of genotype–phenotype relationships as well as assays using banked plasma to validate novel diagnostic tests. Once we can more accurately define HAE with normal C1INH, the registry will be invaluable in learning more about the natural history of the disease and its response to treatments. Patients with HAE with normal C1INH are being actively encouraged to join the registry and participate. We anticipate that the U.S. HAE Association Registry and Bio-Repository, as well as other registries, will become important tools in reaching the goals of improved understanding of HAE with normal C1INH.

In conclusion, we have reached a consensus regarding a working definition of HAE with normal C1INH that identifies patients with a high likelihood of having this disease. A clear subgroup of these patients has an *F12* mutation that cosegregates with the clinical manifestations. Important clinical features of HAE with normal C1INH have been defined, but they are not diagnostic of themselves. We have identified a series of short-term and long-term goals that need to be accomplished to improve the diagnosis and treatment of HAE with normal C1INH as well as sporadic bradykinin-mediated angioedema of unknown cause. Finally, we recognize that the definitions and terminology will need to be updated as progress is made in unraveling these diseases. The task ahead will be to carefully define the clinical problem, lay out the necessary next steps, and conduct the laboratory and clinical research to address these issues for patients with both HAE with normal C1INH and recurrent angioedema of unknown cause. With this approach, we will advance toward the goal of controlling attacks of angioedema and thereby improving the life quality of affected patients.

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